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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/063,592	05/03/2002	Audrey Goddard	P3230R1C001-168	4535

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EXAMINER	
KAUFMAN, CLAIRE M	

ART UNIT	PAPER NUMBER
1646	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action Before the Filing of an Appeal Brief	Application No. 10/063,592	Applicant(s) GODDARD ET AL.	
	Examiner Claire M. Kaufman	Art Unit 1646	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 06 September 2005 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☐ The period for reply expires _____ months from the mailing date of the final rejection.
   b) ☒ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: 1-5.
   Claim(s) withdrawn from consideration: _____.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: See attached.
12. ☒ Note the attached Information Disclosure Statement(s). (PTO/SB/08 or PTO-1449) Paper No(s). 4/13/05,7/13/05,9/6/05.
13. ☐ Other: _____.

Continuation of PTO-303 Advisory Action.

11. The request for reconsideration has been considered but does NOT place the application in condition for allowance because: Most of Applicants' arguments were previously addressed and remain unpersuasive for the reasons of record. Only arguments not previously presented will be addressed here.

Applicants argue on page 4 of the response that the Examiner has made new arguments, cited two new references and is relying on asserted facts not relied upon in the previous Office action. The argument has been fully considered, but is not persuasive. The Examiner's response was only addressing those arguments put forth by Applicants in response to the previous Office action. No new references were added to the rejection. The grounds of rejection remained exactly the same as originally set forth. The references cited by the Examiner were presented to support and explain the Examiner's position and not to make a new grounds of rejection, just as the references cited after first action by Applicants were presented to support and explain Applicants' position. The Examiner has not prematurely cut off prosecution, but has simply answered Applicants' arguments, adding explanation and support as appropriate.

Applicants argue on page 11 of the response to the final action that because the polynucleotide of SEQ ID NO:81 has utility, the differential expression data of the polynucleotide is not in question and the Examiner's statement about critical information lacking, such as significance of differential expression and under what circumstances the differences could be detected, is moot. The argument has been fully considered, but is not persuasive. While the rejection for lack of utility of the PRO1557 polynucleotide was withdrawn, the enablement rejection was maintained. Some of the reasons include the lack of information, guidance or direction to allow the skilled artisan to use the polynucleotide without undue experimentation. It is also maintained in the instant case that regardless of the utility of the encoding polynucleotide, the encoded protein and its cognate antibody do not have utility and are not enabled because it is not reasonably predictable that the encoded protein has an expression pattern corresponding to that of the encoding polynucleotide. Even if it did, there was still be a lack of enablement for how to use the protein and binding antibody for the reasons of record.

Applicants argue (p. 14) that the PTO has issued several patents claiming differentially expressed polypeptides and antibodies. Each application is examined on its own merits. No comment can be made on the patentability of the cited patents. Currently, the instant application has rejections that must be overcome before the claims are allowable.

Applicants argue that the issues relating to the reference of Wu et al. (Gene 311:105-110, 2003) are moot since the utility of the PRO1557 polynucleotide is now accepted. The argument has been fully considered, but is not persuasive. The reference relates to use of the polynucleotide and antibody and is still pertinent. As stated in the previous Office action on p. 9, end of first paragraph, "Also, the teachings of Wu et al., which were published after the filing of the instant application, cannot make up for the insufficiencies of the instant specification relating to lack of enablement of the instant invention for the reasons discussed in the previous Office action and above." Even though the BNF-1 polynucleotide of Wu et al. and the PRO1557 polynucleotide encode identical proteins, there are discrepancies between the differential expression found by Wu et al. and disclosed by the instant application (EXAMPLE 18), despite very low levels of differences being detectable by Wu et al. That there is differential expression of the polynucleotide encoding PRO1557 in kidney and esophageal tumors as asserted by Applicant, the fact that the BNF-1 polynucleotide encoding the same protein was found to be differentially expressed in breast, lung and colon tumor tissues (in which the instant application did not find differential expression), highlights the need for information not provided in the instant application which would help provide guidance or direction to the skilled artisan to be able to use the instant invention without undue experimentation. For example, as stated at the end of the first paragraph on page 8 of the previous Office action, "...without more specifics about necessary sample size, expression level range for normal and tumor tissues, types of kidney or esophageal tissue that can used, and other questions, the specification has not provided the invention in an enabling form."

Applicants argue (pp. 14-15) that the report of Haynes et al. and Gygi et al. (Mol. Cell. Biol., 1999) do not support the Examiner's position that mRNA levels do not correlate with protein levels, pointing out that Haynes did not look at *single* genes and corresponding protein level. The argument has been fully considered, but is not persuasive. A complete reading of Haynes and Gygi et al. continues to support the reliance on Haynes et al. Applicants' point to

the correlation coefficient of 0.935 in Haynes et al., saying that this shows a correlation instead of the lack of one. However, a full reading of Haynes et al. clarifies the data (p. 1726, first full paragraph):

> For the entire group (106 genes) for which a complete data set was generated, there was a general trend of increased protein levels resulting from increased mRNA levels. The Pearson product moment correlation coefficient for the whole data se (106 genes) was 0.935. This number is highly biased by a small number of genes with very large protein and message levels. A more representative subset of the data is shown in the inset of Fig. 5. It shows genes for which the message level was below 10 copies/cell and includes 69% (73 of 106 genes) of the data used in the study. The Pearson product moment correlation coefficient for this data set was 0.356.

Contrary to Applicants' assertion that Figures 5 and 6 of Gygi support the correlation of mRNA and protein levels, Gygi et al. show in Figure 5 the same figure as Fig. 1 of Haynes and show in Fig. 6, what is described for the Pearson correlation coefficients in the cited paragraph above. Gygi et al. say beginning in the last sentence in col. 1 of p. 1727 that, "The observed level of correlation between mRNA and protein expression levels suggest the importance of posttranslational mechanisms controlling gene expression. Such mechanisms include translational control .. and control of protein half-life.... Since these mechanisms are also active in higher eukaryotic cells, we speculate that there is no predictive correlation between steady-state levels of mRNA and those of protein in mammalian cells." As to correlation of an individual gene, Gygi et al. and Haynes et al. point to a great unpredictability about expression of a nucleic acid and its encoded protein. Predicting a correlation for any single gene is more difficult than for a large pool of genes showing a general trend. This can be seen by the low 0.356 correlation coefficient described above by Haynes et al. Each point in the figures of Haynes et al. and Gygi et al. are individual genes (see Fig. 1 and Figs. 5-6, respectively). Therefore, the authors did examine single genes. Haynes et al. supports the rejections of record and also says that the results are expected to be representative for mammalian cells (*e.g.*, like the human cell from which the PRO1557 nucleic acid was isolated).

Applicants argue (pages 16-17) that Fessler et al. shows that in 5/6 cases for which change in mRNA levels was reported, the change corresponded to change in protein level. Also, nothing in the results of Fessler suggests that a change in the level of mRNA for a particular protein does not generally lead to a corresponding change in level of the encoded protein, thus

supporting Applicants assertions. For 6 samples in Table VIII of Fessler, mRNA was "absent" so that correlation with protein is not applicable. Applicants state that, "Nothing in these results by Fessler suggest that a change in the level of mRNA for a particular protein does not generally lead to a corresponding change in the level of the encoded protein." The argument has been fully considered, but is not persuasive. As noted by Applicants (middle of third paragraph, p. 16 of response), "Of 13 up-regulated proteins, a change in mRNA levels is reported in only 3 such proteins. For these 3, mRNA levels were increased in 2 and decreased in the third. Of the 5 down-regulated proteins, a change in mRNA is reported for 3 such proteins. In all 3, mRNA levels are also decreased." Also, of the 13 up-regulated proteins, 5 corresponding mRNAs were unchanged and 5 were not detected ("absent"). That means, disregarding the undetectable mRNAs, for 8 up-regulated proteins, only 2/13 showed corresponding upregulation in mRNA levels. The odds were slightly better for the 5 down-regulated proteins, with 3 corresponding mRNAs also down-regulated, 1 unchanged and 1 detectable ("absent"). So 3/5 down-regulated proteins showed corresponding down-regulation in mRNA levels. (See paragraph bridging cols. 1-2 of p. 31295 of Fessler for data.) One can hardly conclude that the results of Fessler support that the change in levels of particular encoding mRNAs generally leads to a corresponding change in levels of the proteins. Indeed, what the results of Fessler et al. show is that a change in mRNA level does not necessarily have a corresponding change in protein levels and *vice versa*. This supports the high unpredictability for correspondence of protein and mRNA levels. When the findings of Fessler et al. are viewed with the findings of others such as Hayes et al. (previously cited) in the relatively new field of proteomics, the "...art does not provide a reasonable expectation that expression of the nucleic acid of SEQ ID NO:81 positively correlates with the expression of the protein of SEQ ID NO:82. The advent of proteome analysis has begun to elucidate the reality of nucleic acid and protein expression which is becoming recognized as more complicated and different from the previously accepted dogma." (p. 5, middle, previous Office action)

Applicants argue (p. 17-18) that the 2-D PAGE technique used by Fessler et al. is selective for proteins with particular characteristics and tends to select more abundant protein species. The argument has been fully considered, but is not persuasive. To avoid the problems associated with lowered sensitivity of their technique, Fessler et al. used only those spots which

were common to all twelve pH3.0-10.0 two-D gels and which met statistical significance criteria (p. 31301 end of first full paragraph). The findings in general show that post-transcriptional and –translational modifications play an important role in biological influence of the encoding nucleic acid and encoded protein (*e.g.*, p. 31301, middle of last paragraph). The reference reinforces the complexity of translational factors and supports the warning concerning the inability to drawing conclusions about protein levels based on mRNA levels.

Applicants argue (top of p. 21) that the PTO dismissed the declarations and publications submitted by Applicants, relying only on the specification as originally filed." The argument has been fully considered, but is not persuasive. None of the declarations or publications was "dismissed", but were addressed by the Examiner and found to be insufficient to overcome the rejections for reasons of record (see previous Office action for discussion or declarations and publications submitted by Applicants).

Applicants argue (p. 21) that, "[T]he PTO appears to take the position that additional data and evidence, beyond the evidence already provided Example 18 and the evidence already presented in the Declarations and other exhibits, must be disclosed in order for Applicants to initially establish a utility for the claimed antibodies. Applicants submit that the PTO's prerequisite of additional evidence is beyond that necessary to establish utility." The argument has been fully considered, but is not persuasive. There are a number of significant unknowns in the specification that neither the declarations nor exhibits and arguments overcome. As quoted on page 6 of the previous Office action, "The instant situation is directly analogous to that which was addressed in *Brenner v. Manson*, 148 U.S.P.Q. 689 (Sus. Ct, 1966), in which the court held that:

> "The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility", "[u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field", and "a patent is not a hunting license", "[i]t is not a reward for the search, but compensation for its successful conclusion."

As was stated above, the literature cautions researchers from drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue. Without more

specifics about necessary sample size, expression level range for normal and tumor tissues, the specification has not provided the invention in a form." Other gaps in information include, for example, tumor type (etiology), repeatability of the differential expression both in terms of frequency/prevalence and quantity/sensitivity, and a basis for reasonably expecting that a change in cDNA level causes a corresponding change in protein level. It is maintained that significant further research would be necessary to use the claimed invention.

In arguing enablement under 35 USC 112, first paragraph, Applicants say (p. 26) that the Court held there was "a high level of skill in the art" of making and using antibodies...," and the instant specification provides directions for doing so. The argument has been fully considered, but is not persuasive. If the protein to which a claimed antibody binds is enabled, then the antibody would likewise be enabled. There is no enablement in the instant case for the protein or antibody, however. Binding a protein in kidney or esophagus samples when the significance/function of the protein is not known, does not confer enablement for the binding antibody.

Applicants argue (p. 27) that the need for further experimentation does not make it undue or preclude the invention from being enabled. The argument has been fully considered, but is not persuasive. Applicants are direct to the *Wands* analysis, for example, on pages 3-4 of the previous Office action discussing why it would require undue experimentation to use the claimed invention. As stated in *Brenner v. Manson* (*supra*), a patent "...is not a reward for the search, but compensation for its successful conclusion." It is maintained for the reasons of record that the instant invention is not at a point where specific benefit exists in a currently available form.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Claire M. Kaufman, whose telephone number is (571) 272-0873. Dr. Kaufman can generally be reached Monday, Tuesday, Thursday and Friday from 9:30AM to 2:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached at (571) 272-0829.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Official papers filed by fax should be directed to (571) 273-8300. NOTE: If applicant *does* submit a paper by fax, the original signed copy should be retained by the applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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Patent Examiner, Art Unit 1646
September 27, 2005

LORRAINE SPECTOR
PRIMARY EXAMINER